REMARKS

Applicants have the following comments in support of this amendment.

Entry of Amendment

As a RCE is being filed herewith, this amendment should be entered and considered at this time.

Claim Amendments - Reference To The Disclosure

The Claimed Halogenated Xanthenes Are In Solution

Independent Claims 1, 3, 16, 18, 22, 23, 29, 31, 46, 47 and 50 have been amended to be more explicitly directed to a preferred embodiment of the present application, i.e. intracorporeal radiosensitizer pharmaceutical compositions and medicaments consisting of a *solution* of certain halogenated xanthenes in a pharmaceutical delivery vehicle (e.g. composition consisting of a halogenated xanthene dissolved in a liquid pharmaceutical delivery vehicle). Such amendment overcomes the need for explicit reference in the claims to the presence or absence of a liposome in such radiosensitizer agents since the halogenated xanthenes cannot be both dissolved (i.e., be in solution) and contained in a liposome.

Support for the claimed solutions is found throughout the specification of the present application, including for example the following passage:

> "It is thus a further embodiment of the present invention that at least one halogenated xanthene or halogenated xanthene derivative be formulated as an intracorporeal medicament in a form suitable for intracorporeal administration via various conventional modes and routes. Such suitable forms include medicaments formulated in a

> liquid, semisolid, solid or aerosol delivery vehicle, including aqueous suspensions, non-aqueous suspensions, *solutions*, creams, ointments, gels, syrups, micro-droplet sprays, suppositories, tablets and capsules. The at least one halogenated xanthene or halogenated xanthene derivative *may be dissolved* or suspended *in such delivery vehicle* ..." (p. 15, line 18 - p. 16, line 1, emphasis added)

This passage makes it clear that the claimed halogenated xanthenes may be dissolved in solution, that such solutions are suitable for intracorporeal delivery to tissue, and accordingly that such solutions are suitable for radiosensitization.[1]

Therefore, these amendments to the claims have not added any new matter, and the amendments are clearly supported by the original application as filed. Hence, it is respectfully requested that these amendments be entered and considered at this time.

The Claimed Halogenated Xanthenes Do Not Contain A Radioisotope

In Applicants' amendment of June 8, 2005 (Amendment D), Applicants amended p. 9 of the specification to recite that the halogenated xanthenes of the present invention do not contain a radioisotope and are therefore not radioactive.[2] In support of this amendment Applicants explained that the amended language merely served to clarify this aspect of the claimed invention in unambiguous language, noting that support for the proposed amendment could be found throughout the specification as filed. For example, Applicants noted in Amendment D that:

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[1] Claims 36-38 have been canceled without prejudice or disclaimer in order to advance the prosecution of this application.

[2] Applicants will address the Examiner's specific objection to this amendment from the Final Rejection and comments infra.

(a) the claimed pharmaceutical compositions and medicaments, and all components therein, are not radioactive, since such compositions and medicaments *work in conjunction with separately applied radiation*;

(b) the claimed pharmaceutical compositions and medicaments, and all components therein, *are non-toxic in the absence of applied radiation*, and hence cannot emit ionizing radiation since ionizing radiation is inherently toxic;

(c) since *radiosensitizers are expected to function by absorbing radiation* rather than emitting it, they are by definition non-radioactive;

(d) the molecular weights (mw) listed in Table 1 for the representative halogenated xanthenes exclude all radioisotopes, since such *radioactive analogs would have different molecular weights* than those listed;

(e) the example *molecular structures* shown in Figures 1a and 1b *do not indicate the presence of a radioisotope* in the structure of the halogenated xanthenes; and

(f) the *absence of a designated radioisotope* in the listed chemical formula or name of each example halogenated xanthene *excludes incorporation of radioisotopes* in the claimed halogenated xanthenes.

It is respectfully submitted that these disclosures and reasons are sufficient to support the amendment to the specification. In further support thereof, Applicants are submitting herewith a signed affidavit of Amos Norman, Professor Emeritus in the Department of Radiation Oncology, Geffen School of Medicine, University of California, Los Angeles. Professor Norman is a distinguished pioneer in the field of radiosensitization and an expert on the development of radiosensitizers. Professor Norman is believed to have pioneered the use of radiodense materials

(such as molecules containing halogens) for radiosensitization. As explained in his affidavit, Professor Norman is familiar with patents and the disclosure of the present application.

Professor Norman's affidavit affirms each of Applicants' points enumerated above, supporting Applicants' assertion that the specification as originally filed clearly conveys to one of ordinary skill in the art that the halogenated xanthenes of the present application do not contain a radioisotope and are therefore not radioactive.

Accordingly, the specification, as filed, of the present application clearly supports the amendment to the specification to exclude incorporation of radioisotopes in the halogenated xanthenes of the present invention. Therefore, this amendment to the specification does not add new matter to the application, and it is respectfully requested that this amendment be entered at this time.

Novel Composition of Matter

Amended independent Claims 1, 16, 22, 29, 46 and 47 are directed to various pharmaceutical compositions that contain novel, highly-halogenated halogenated xanthenes (i.e., 4,5,6,7-Tetra-bromoerythrosin, Monobromoerythrosin, Dibromoerythrosin, Tribromoerythrosin, Monochloro-erythrosin, Dichloroerythrosin, Trichloroerythrosin, Monofluoroerythrosin, Difluoroerythrosin, Trifluoroerythrosin, 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein, 2',4,5,6,7,7'-Hexafluorofluorescein, and 4,5,6,7-Tetrafluorofluorescein), none of which are believed to have been described or suggested in the prior art, including that art cited by the Examiner in this or any of the prior actions for this application.

Due to the relative complexity of synthesis of such compounds and other factors, such as photostability considerations, Applicants submit that they are the first to invent the claimed new

compounds which represent a novel extension to the halogenated xanthene family. For example, Rose Bengal (which formerly comprised the most halogen-rich member of the halogenated xanthene family) has been known for over 100 years. Nonetheless, knowledge of its properties and those of the other previously known halogenated xanthenes (such as phloxine B, erythrosin, and eosin) has not led those skilled in the art (prior to Applicants' conception) to conceive, suggest, synthesize or investigate these claimed highly-halogenated halogenated xanthenes. Nor has anyone else appeared to conceive of pharmaceutical compositions consisting of halogenated xanthenes for any radiosensitization use prior to Applicants' work.

Applicants conceived of these new compounds in an effort to improve their fundamental radiosensitizer invention, the performance of which may be enhanced by increasing the radiodensity of the halogenated xanthene molecules, for example by including greater numbers of halogen atoms or increasing their atomic number. This is illustrated by the following passage from the specification of the present application:

> "Since the radiation cross-section of halogens increases substantially in the order F < Cl < Br < I (as shown in Figure 2), it is further preferred that this medicament include, as a radiodense ingredient, those halogenated xanthenes with a large content of I or Br." (p. 10, lines 20-22)

Since such considerations are irrelevant with regard to the optical properties of the halogenated xanthenes (i.e., the optical properties of the halogenated xanthenes are similar regardless of halogen content), investigators (such as Heitz, Johansson, or Crounse, as cited by the Examiner in the present Office Action) were not motivated to consider or investigate, and there is no evidence that they conceived of or considered, such novel compounds since these compounds would have no obvious relevance for the photodynamic uses employed by such investigators.

Accordingly, Applicants respectfully submit that the claimed highly-halogenated halogenated xanthenes, and the various claimed pharmaceutical compositions containing such highly-halogenated halogenated xanthenes, of the claims of the present application are novel over the prior art.

Response to Final Rejection

Applicants appreciate the Examiner's withdrawal of many of the prior objections and rejections.

Applicants will now address each of the Examiner's remaining objections, rejections and comments in the order in which the rejections appear in the Final Rejection.

Specification – 35 USC §132(a)

In the Final Rejection, the Examiner objects to Applicants' amendment of p. 9 of the specification under 35 USC §132(a) for alleged introduction of new matter into the disclosure. This rejection is respectfully traversed.

For at least the reasons explained supra, the amendment to the specification does not introduce any new matter. Further, as explained below in response to the §112, first paragraph rejection, the Examiner's reasons, comments and case citation in support of this objection is not persuasive. Accordingly, it is respectfully requested that this objection be withdrawn, and the amendment of p. 9 of the specification be entered and allowed.

Claim Rejections – 35 USC §112

35 USC §112, second paragraph; 35 USC§101

The Examiner also rejects Claims 16-18, 20 and 21 under 35 USC §112, second paragraph, as being indefinite and under 35 USC §101 as reciting a use without reciting any steps. This rejection is also respectfully traversed.

While Applicants traverse this rejection, in order to advance the prosecution of this application, independent Claims 16 and 18 has been amended to recite wherein said halogenated xanthene is dissolved in said pharmaceutical delivery vehicle to form said medicament. Further amendments have been much made to correct informalities in claim language. It is respectfully submitted that these amendments overcome the Examiner's objections, and it is respectfully requested that these rejections be withdrawn.

35 USC §112, first paragraph

The Examiner also rejects Claims 1-3, 11-14, 16-18, 20-23, 25-31, 36-40 and 46-50 under 35 USC §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner contends that there is no literal or adequate descriptive support for the recitation of "said halogenated xanthene does not contain a radioisotope" and "said composition does not contain liposomes" in the claims. This rejection is also respectfully traversed.

With regard to the rejection based on language in independent Claims 1, 3, 16, 18, 22, 23, 29, 31, 46, 47 and 50 that exclude radioisotopes, as described supra, this language is supported by Applicants' amendment of the specification on p. 9. Further, as explained supra, there is clear support in the specification for this limitation in the claim language. As evidenced by the affidavit

of Professor Norman, one of ordinary skill in the art reading the specification of the present application would clearly understand that the claimed halogenated xanthenes do not contain a radioisotope (even without the language of amendment to page 9 of the specification). Hence, this feature clearly flows from Applicant's disclosure, and there is clear support for this claimed limitation in the application as filed.

Furthermore, in support of her rejection (and objection to the amendment of the specification), the Examiner cites In re Anderson, 176 USPQ 331 (CCPA 1973). This case does not support the Examiner's contentions in this case.

More specifically, a new matter rejection, such as the Examiner makes herein, is discussed at 176 USPQ 336 of Anderson. In that section, the Examiner rejects the claim for amending the term "containing" to "carrying" as being new matter. The Court recognizes that the term "carrying" does not appear in the specification. The Court, however, states that

> "[t]he question, as we view it, is not whether 'carrying' was a word *used* in the specification as filed but whether there is *support* in the specification for employment of the term in a claim; is the concept of carrying present in the original disclosure?" (emphasis in original).

The Court found that there was support for the claimed term in the disclosure, despite the specification not reciting this term, and would not sustain the new matter rejection. Similarly, as explained above, the specification of the present application clearly supports this limitation.

An even more analogous situation is presented in In re Parks, 30 USPQ2d 1234 (Bd Pat App & Int. 1993) wherein the Board of Patent Appeals stated that:

> "We are not unmindful of the decision in Ex parte Grasselli, 231 USPQ 393 (Bd.App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984), which involved claims to a process for the ammoxidation of propane or isobutane employing a catalyst "free of uranium and the combination of vanadium and phosphorus." Under the particular

facts in that case, it was held that the negative limitation introduced new concepts in violation of the description requirement of the first paragraph of 35 U.S.C. 112, citing In re Anderson, supra. In the situation before us, n3 it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art that appellants had possession of the concept of conducting the decomposition step generating nitric acid in the absence of a catalyst. See, for example, column 5 of the '562 patent, first paragraph, wherein FIG. 4 is discussed. Pyrolysis temperatures of between 600 degrees C and 700 degrees C, and above 700 degrees C were employed to achieve conversion of chemically bound nitrogen to nitric oxide. Smooth conversion was obtained above 700 degrees C, while the optimum conversion was found to occur above 900 degrees C. Throughout the discussion which would seem to cry out for a catalyst if one were used, no mention is made of a catalyst. n4

n3 Whether the requirement for an adequate written description has been met is a question of fact and, hence, driven by the exigencies of each case. Wang Laboratories, Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

n4 A "catalyst" normally functions to accelerate a particular reaction. See for example, Hawley, Condensed Chemical Dictionary, Tenth Edition, 1981, pp. 205 and 206, copies of which are enclosed for appellants' convenience and made of record.

Moreover, according to two declarations by Wentworth, a professor of chemistry at the University of Houston, whose expertise in this particular art has not been challenged, one having ordinary skill in the art would have recognized that the reaction generating nitric oxide, according to the equation disclosed in the '562 patent, is conducted without a catalyst. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); In re Lemin, 364 F.2d 864, 150 USPQ 546 (CCPA 1966). Thus, it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art the concept of effecting decomposition at an elevated temperature in the absence of a catalyst. In re Anderson, supra.

Accordingly, the examiner's rejection of claims 1 through 10, 20 through 22 and 55 through 80 under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support is reversed."

In accordance with this precedence and supported by the affidavit of Professor Norman, the disclosure in the present application as filed clearly conveys to one of ordinary skill in the art the

claimed halogenated xanthenes do not contain a radioisotope. Hence, the §112 rejection for lack of adequate descriptive support for this limitation should be withdrawn.

With regard to the rejection based on the language regarding excluding liposomes, although Applicants traverse this rejection, in order to advance the prosecution of this application, independent Claims 1, 3, 16, 18, 22, 23, 29, 31, 46, 47 and 50 have been amended to be more explicitly directed to a preferred embodiment of the present application, i.e. intracorporeal radiosensitizer pharmaceutical compositions and medicaments consisting of a *solution* of certain halogenated xanthenes (dissolved in) in a pharmaceutical delivery vehicle. Such amendment overcomes the need for explicit reference to the presence or absence of a liposome in such radiosensitizer agents from the claim language, since the halogenated xanthenes cannot be both dissolved (i.e., be in solution) and contained in a liposome.[3] As described supra, the rejected independent claims have been amended, removing the negative limitation excluding liposomes, and thereby rendering this rejection moot.

Accordingly, it is respectfully requested that the rejection of the claims under §112, first paragraph, be withdrawn.

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[3] Applicants note that the amended claims maintain exclusion of liposomes from the presently claimed radiosensitizer compositions and medicaments without requiring the objected to negative limitation. Specifically, it is clear from the definition of a liposome that the solutions in the claimes exclude liposomes from the claimed compositions and medicaments. For example, according to a standard medical dictionary (Stedman's Medical Dictionary, 27th Edition, Lippincott Williams & Wilkins, Philadelphia, 2000, p. 1022, attached), a liposome is defined as:

> "1. A spherical particle of liquid substance suspended in an aqueous medium within a tissue. 2. Any small, roughly spherical artificial vesicle consisting of a lipid bilayer enclosing some of the suspending medium."

Thus, the presently claimed radiosensitizer compositions and medicaments, comprising an solutions of a halogenated xanthene, cannot contain liposomes since if they did such compositions and medicaments would thereby comprise suspensions instead of solutions.

Claim Rejections – 35 USC §102

Heitz et al.

The Examiner also rejects Claims 1, 11-14, 16, 17, 20, 21, 29, 36-40 and 46-49 under 35 USC §102(b) as being anticipated by Heitz et al. (USP 4,846,789). This rejection is also respectfully traversed.

In particular, and contrary to the Examiner's contentions, Heitz simply does not disclose or suggest the novel, highly-halogenated halogenated xanthenes recited in independent Claims 1, 16, 29, 46 and 47. The Examiner appears to be contending that the halogenated xanthene dyes in Heitz can be manipulated to arrive at the claimed halogenated xanthenes. However, such manipulation and modifications are not an anticipation of the claimed compositions. Further, as explained supra, the claimed compositions are novel. Furthermore, as explained supra and below, one of ordinary skill in the art would not make the Examiner's manipulation and modifications of the halogenated dyes to arrive at the claimed invention, and there is no motivation for one of ordinary skill in the art to make such modifications. Accordingly, since Heitz fails to teach or suggest the existence of the claimed halogenated xanthenes (such as 4, 5, 6, 7-Tetrabromoerythrosin), Heitz cannot anticipate nor render obvious the claimed invention. Hence, it is respectfully requested that the rejection of these claims and those claims dependent thereupon be withdrawn.

Additionally, Heitz is concerned with certain optical properties of *known* halogenated xanthenes, and thus provides no motivation for conceptualization or investigation of the highly-halogenated molecules of independent Claims 1, 16, 29, 46 and 47.

Second, as Applicants explained in detail in Amendment D, Heitz does not disclose or suggest the presently claimed therapeutic compositions, medicaments or uses. Instead of teachings directed to pharmaceutical compositions for treatment of diseases of human and animal tissue (as

is the subject of Applicants claimed invention), Heitz is directed to *pesticidal compositions and uses* (i.e., *ex vivo* killing of intestinal parasites to prevent infection, wherein the pathogenic organisms are killed by exposure to light outside of the infected animal before they can infect another animal).

Accordingly, the disclosure in Heitz does not therapeutically affect the animal to which the photosensitive dye is fed, but rather serves to break the chain of transmission of pathogens from one infected animal to another once the pathogens are exposed to light outside of the host animal's body, and is not relevant to the present invention. Therefore, the disclosure in Heitz is not directed nor does it disclose or suggest an injectable radiosensitizer pharmaceutical composition (as required in Claim 1 in the present application); nor does it comprise use of a dye in the preparation of an intracorporeal radiosensitizer medicament (as required in Claim 16); nor is it a radiosensitizer pharmaceutical composition (as required in Claims 29 and 47); nor is it even an intracorporeally-applicable radiosensitizer medicament (as required in Claim 46).

Third, Heitz does not disclose or suggest applied ionizing radiation having an energy of greater than approximately 1 keV, as required in independent Claims 1, 16, 29, 46 and 47. Instead, as noted by the Examiner on p. 7 of the Final Rejection, Heitz discloses use of light energy, including visible light, near infrared light, and near to far ultraviolet light. Such light has energy far below the 1 keV recited in the independent claims and underlies the fundamental reason why the disclosure in Heitz requires exposure of pathogens to light energy outside of the body (such light cannot penetrate into the body), whereas Applicants' claimed invention allows delivery of activating energy (i.e., highly penetrating ionizing radiation) to any location within the body, thereby allowing disease to be treated in situ. In fact, Heitz makes no disclosure or suggestion of any interaction of any sensitizing agent with ionizing radiation, and therefore completely misses the topic of radiosensitization and is not in any way relevant to the present invention.

Since Heitz fails to teach or suggest the recited halogenated xanthenes, the ionizing radiation energy levels, the fundamental properties, and mechanisms of the claimed radiosensitizer pharmaceutical compositions, medicaments, and uses, Heitz cannot anticipate nor render obvious the claimed invention of the present application.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions, the medicaments or uses of the independent claims of the present application. Accordingly, the claims of the present application are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §103

Heitz et al.

The Examiner also rejects Claims 2, 22, 25-28 and 30 under 35 USC §103(a) as being anticipated by Heitz. This rejection is respectfully traversed.

First, as described supra with regard to the §102 rejection, Heitz does not disclose or suggest the novel, highly-halogenated halogenated xanthenes recited in independent Claims 1, 22 and 29. Since Heitz fails to teach or suggest the existence of these halogenated xanthenes (such as 4, 5, 6, 7-Tetrabromoerythrosin), Heitz cannot render obvious the claimed invention of rejected Claims 2, 22, 25-28 and 30.

Second, the Examiner cites "result effective variables" as a basis for this rejection, including activation energy (i.e., the ionizing radiation having an energy greater than 1 keV of the present invention vs. the optical energy of Heitz) and concentration of halogenated xanthene. The Examiner alleges that optimal values for such variables could be discovered by routine experimentation. Applicants respectfully traverse this position for several fundamental reasons.

In particular, the U.S. Patent Office has granted to Applicants U.S. patents for inventing methods of radiosensitization using halogenated xanthenes (USP 6,331,286) and methods of radiosensitization using intracorporeal radiosensitizers that incorporate novel, highly-halogenated halogenated xanthenes (USP 6,991,776), including those of the claims of the present application. These patents illustrate the fundamental novelty of Applicants' use of such compounds in radiosensitizer pharmaceutical compositions and medicaments. This novelty is particularly notable given the extensive history of study directed on the halogenated xanthene family. Specifically, despite over a century of intense study of various halogenated xanthenes by numerous investigators, prior to Applicants' work, no one has contemplated, nor discovered through routine experimentation, any use of any halogenated xanthene with ionizing radiation having an energy greater than of Applicants' claimed range of 1 keV.[4] Since the optical energy of Heitz and other investigators is well outside the range of electromagnetic radiation claimed by Applicants, conceiving the use of such ionizing radiation having an energy of 1 keV or greater requires inventive insight and cannot be the mere result of routine experimentation. The band of optical energy of Heitz simply does not overlap that of the energy utilized by Applicants, so no amount of routine experimentation with such optical energy would lead to discovery or use of the ionizing energy claimed by Applicants.

Additionally, Heitz is silent on the matter of concentration of halogenated xanthene in any hypothetical medicament. In contrast, Applicants' claimed range of 0.001% to 20% has been discovered to provide effective interaction with applied ionizing radiation. Since, as described supra, one of ordinary skill in the art would not be led to utilize such applied ionizing radiation based on

[4] The known prior art, such as Neckers, which is of record, concerns use of energies much more than a factor of 100 lower than 1 keV. Similarly, the energies of Heitz are more than a factor of 100 lower than 1 keV.

the teachings in Heitz, routine experimentation would not lead to Applicants' claimed invention or the preferred concentration ranges.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions and medicaments of the present application, and the claimed range is not the result of routine experimentation. Accordingly, the claims of the present application are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Johansson and Crounse

The Examiner also rejects Claims 3, 18, 23, 31 and 50 under 35 USC §103(a) as being unpatentable over Johansson (Svensk Farmaceutisk Tidskrift, 1973) or Crounse et al. (USP 4,647,578). This rejection is also respectfully traversed.

As noted by the Examiner on p. 10 of the Office Action, neither Johansson nor Crounse disclose or suggest the disodium salts of the halogenated xanthenes as recited in independent Claims 3, 18, 23, 31 and 50. The Examiner, however, contends that these would be obvious variations. Applicants respectfully disagree.

Instead, Johansson and Crounse describe other chemical forms of Rose Bengal: Johansson describes a mono-sodium form of Rose Bengal (RB^-) while Crounse describes a free acid form. Both of these forms have completely different chemical properties compared with the disodium forms claimed in the present application. Because the acid dissociation constants (pKa) of Rose Bengal are approximately 3.7 and 4.8, pertaining to the following equilibria:

$$RB \text{ (free acid)} \rightleftharpoons RB^- + H^+ \qquad pKa_1 = 3.7$$

$$RB^- \rightleftharpoons RB^{2-} + H^+ \qquad pKa_2 = 4.8$$

the free acid and mono-sodium (i.e., monobasic) forms of Rose Bengal yield acidic compositions whereas the disodium (i.e., dibasic) form of Rose Bengal (i.e., RB^{2-}) of Claims 3, 18, 23, 31 and 50 yields a neutral composition. Applicants have found through detailed experimentation that such neutral compositions exhibit targeting of diseased tissue as described in the specification of the present application, whereas acidic compositions appear not to provide such targeting. Accordingly, the forms of Rose Bengal described in both Johansson and Crounse differ from that claimed in Claims 3, 18, 23, 31 and 50, both in chemical composition and functional activity. Hence, neither Johansson nor Crounse, taken alone or in any hypothetical combination, disclose or suggest the claimed invention.

Moreover, on page 10 of the Final Rejection, the Examiner alleges that "it would have been obvious to one of skill in the art ... to substitute disodium forms of Rose Bengal or other halogenated xanthenes into the teaching of Johansson or Crounse...." See also page 14. Assuming arguendo that such substitution was made (which Applicants submit is improper and would not be made by one skilled in the art as explained above), the alleged hypothetical skilled practitioner would still fail to arrive at the claimed invention since neither Johansson nor Crounse contain any teaching of relevance to the subject of radiosensitization.

For example, Johansson discusses purification of Rose Bengal for use in certain diagnostic pharmaceuticals known at the time.[5] Such diagnostic pharmaceuticals are not radiosensitizers and are not suitable as radiosensitizers, so any substitution of other chemical forms of Rose Bengal into the disclosure of Johansson fails to produce the claimed invention.

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[5] Radiosensitization using Rose Bengal or any other halogenated xanthene was first taught by Applicants nearly 30 years after publication of Johansson.

Similarly, Crounse discusses certain pesticidal compositions containing Rose Bengal, such compositions being in diametric opposition to the intracorporeal therapeutic compositions of the claimed invention. Such pesticidal compositions are not radiosensitizers and are not suitable as radiosensitizers, so any substitution of other chemical forms of Rose Bengal into the disclosure of Crounse fails to produce the claimed invention.

Accordingly, the teachings of Johansson and Crounse, whether taken together or separately, are not relevant to the patentability of the claimed radiosensitizer compositions and medicaments, nor to the claimed details concerning these compositions.

For at least the above-stated reasons, Applicants respectfully submit that even if combined, the cited references fail to disclose or suggest the claimed invention. Therefore, it is respectfully requested that this rejection be withdrawn.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this Amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: February 23, 2006

Mark J. Murphy
Registration No. 34,225

COOK, ALEX, McFARRON, MANZO,
CUMMINGS & MEHLER, Ltd.
200 West Adams Street, Suite 2850
Chicago, Illinois 60606
(312) 236-8500

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teinemia. Medical management of patients with coronary artery disease (myocardial infarction, angina pectoris, history of coronary artery bypass graft or coronary angioplasty) and other atherosclerotic disorders (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease) includes detection and correction of hypercholesterolemia and hyperlipoproteinemia. Reducing elevated LDL cholesterol diminishes the risk of coronary artery disease; besides halting the progression of atherosclerosis, it may even shrink established atherosclerotic lesions. Of persons with elevated LDL cholesterol, 75% can achieve normal levels with diet, weight reduction, and exercise; the remainder need drug treatment. Factors besides familial hyperlipoproteinemias that can elevate LDL cholesterol include diabetes mellitus, hypothyroidism, nephrotic syndrome, obstructive liver disease, and drugs (progestogens, anabolic steroids, corticosteroids, thiazide diuretics). Dietary saturated fat raises LDL cholesterol more than any other dietary component, cholesterol itself not excepted.

l. (a), a l. consisting of an LDL particle to which a large glycoprotein, apolipoprotein (a), is covalently bonded. Elevation of the concentration in serum has been identified as a risk factor for coronary artery disease.

Elevation of plasma lipoprotein (a) above 30 mg/dL is a strong independent risk factor for coronary artery disease and possibly for stroke. A unique feature of lipoprotein (a) is the structural similarity of its nonlipid moiety, apolipoprotein (a), to plasminogen. This similarity allows it to bind to endothelium and to proteins of cellular membranes. It inhibits fibrinolysis by competing for plasminogen binding sites and also favors lipid deposition and stimulates smooth muscle cell proliferation. Niacin and estrogen lower Lp(a), but HMG-CoA reductase inhibitors, fibrates, and bile acid sequestrants do not.

α_1-l., A lipoprotein fraction of relatively low molecular weight, high density, rich in phospholipids, and found in the α_1-globulin fraction of human plasma.

β_1-l., A lipoprotein fraction of relatively high molecular weight, low density, rich in cholesterol, and found in the β-globulin fraction of human plasma.

intermediate density l. (IDL), class of l.'s formed in degradation of very low density l.'s; about half are cleared quickly from the plasma into the liver by receptor-mediated endocytosis; the other half are degraded into low density lipoproteins.

l. Lp(a), a l. composed of an LDL particle combined with an additional protein, Lp(a) specific protein; elevated levels have been identified as a risk factor for coronary artery disease; elevations may be treated with niacin.

malondialdehyde-modified low-density l., IDL molecule with aldehyde-substituted lysine residue(s) in the apoprotein moiety, resulting from oxidative reaction accompanying prostaglandin synthesis and platelet aggregation.

l.-X, An abnormal low-density lipoprotein found in patients with obstructive jaundice.

lip·o·pro·tein li·pase. An enzyme that hydrolyzes one fatty acid from a triacylglycerol; its activity is enhanced by heparin and inactivated by heparinase. It is activated by apolipoprotein C-II; a deficiency of l. l. is associated with familial hyperlipoproteinemia type I. SEE ALSO familial lipoprotein lipase *inhibitor*, clearing *factors*, under *factor*. SYN diacylglycerol lipase, diglyceride lipase.

lip·o·sar·co·ma (lip'ō-sar-kō'mă). A malignant neoplasm of adults that occurs especially in the retroperitoneal tissues and the thigh, usually deep in the intermuscular or periarticular planes; histologically, l. is a large tumor that may be composed of well-differentiated fat cells or may be dedifferentiated, either myxoid, round-celled, or pleomorphic, usually in association with a rich network of capillaries; recurrences are common, and dedifferentiated l. metastasizes to the lungs or serosal surfaces. [lipo- + *sarx*, flesh, + *-oma*, tumor]

li·po·sis (li-pō'sis). **1.** SYN adiposis. **2.** Fatty infiltration, neutral fats being present in the cells. SEE ALSO lipolipoidosis. [lipo- + G. *-osis*, condition]

li·pos·i·tol (lip-os'i-tol). SYN inositol.

lip·o·sol·u·ble (lip-ō-sol'ū-bl). Fat-soluble.

lip·o·some (lip'ō-sōm). **1.** A spherical particle of lipid substance suspended in an aqueous medium within a tissue. **2.** Any small, roughly spherical artificial vesicle consisting of a lipid bilayer enclosing some of the suspending medium. [lipo- + G. *sōma*, body]

lip·o·suc·tion (lip'ō-sŭk-shun). Method of removing unwanted subcutaneous fat using percutaneously placed suction tubes.

tumescent l., l. performed after subcutaneous infusion of lidocaine solution and the use of microcannulae.

wet-technique l., l. performed after subcutaneous infusion of dilute epinephrine solution.

lip·o·suc·tion·ing (lip'ō-sŭk'shŭn-ing). Removal of fat by high vacuum pressure; used in body contouring.

lip·o·thi·am·ide py·ro·phos·phate (lip-ō-thī'am-īd). Name once given to the coenzymes of the multienzyme complex catalyzing the formation of acetyl-CoA from pyruvate and involving lipoamide and thiamin pyrophosphate, on the assumption that they were a single compound. SEE lipoic acid.

lip·o·tro·phic (lip-ō-trof'ik). Relating to lipotrophy.

li·pot·ro·phy (li-pot'rō-fē). An increase of fat in the body. [lipo- + G. *trophē*, nourishment]

lip·o·tro·pic (lip-ō-trop'ik). **1.** Pertaining to substances preventing or correcting excessive fat deposits in liver such as occurs in choline deficiency. **2.** Relating to lipotropy.

lip·o·tro·pin (li-pō-trō'pin). A pituitary hormone mobilizing fat from adipose tissue. β-L. is a single-chain peptide of 91 amino acyl residues that contains the sequences of endorphins, metenkephalin, and β-melanotropin; γ-l. is shorter and is identical in sequence to the N-terminal 58 residues of β-lipotropin; both contain sequences common to ACTH and β-melanotropin. SYN lipid-mobilizing hormone, lipotropic hormone, lipotropic pituitary hormone.

plasma lipoproteins

	density (g/ml)	diameter (nm)	apoproteins	%	%	%
chylomicrons	<0.95	90–1000	A-1, A-2, B-48, C-2, C-3, E	1–2	88	4
very low-density lipoproteins (VLDL)	0.95–1.006	30–90	B-100, C-1, C-2, C-3, E	7–10	56	23
intermediate-density lipoproteins (IDL)	1.006–1.019	25–30	B-100	11	43	29
low-density lipoproteins (LDL)	1.019–1.063	20–25	B-100	21	58	13
high-density lipoproteins (HDL)						
HDL_2	1.063–1.125	10–20	A-1, A-2, A-4, C-1, C-2, C-3, D	33	41	16
HDL_3	1.125–1.210	7.5–10		57	35	13